Fertility preserving treatments in different prognostic groups of cervical cancer patients

Ph.D thesis

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Original papers the Ph.D. thesis based on:

I. Balazs Lintner, Srdjan Saso, Laszlo Tarnai, Zoltan Novak, Laszlo Palfalvi, Giuseppe Del Priore, J Richard Smith, Laszlo Ungar
Use of Abdominal Radical Trachelectomy to treat Cervical Cancer greater than 2cm in diameter
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II. Ungar L, Palfalvi L, Tarnai L, Nechushkina V, Lintner B, Novak Z
Surgical Treatment of Stage IB Cervical Cancer
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Original papers not related to the topic:

Bátorfi József, Kónya Márton, Hajdu Krisztina, Gasztonyi Zoltán, Lintner Balázs, Bacsó Erika, Pecsérke Marianna, Varga Tünde
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Szabó I, Sobel G, Lintner B, Schaff Zs, Paulin F
Praesacralis utóbélcysta
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Summery of the thesis

1. In this study, we report the fertility treatment approaches in the different prognostic groups of patients. The initial steps and the vaginal radical trachelectomy (VRT), as the first method is reported. VRT is a worldwide accepted, oncologically safe procedure in retaining the fertility of a special group of cervical cancer patients.

2. We introduce the abdominal radical trachelectomy (ART) and our initial experience with 30 operated patients. The radicality of the procedure can be identical to that of a traditional type III Wertheim hysterectomy. Technically it's easily adopted by surgeons having experience in radical hysterectomy. Obstetrical outcomes are similar to those of the historical vaginal radical trachelectomy cohorts.

3. Tumor size is an important criterion for fertility preservation surgery in most centers. Oncology outcomes are reported acceptable if the tumor does not exceed 2 cm in diameter. VRT and ART are generally considered oncologically safe under the limit of 2 cm tumor size. Recurrences in tumors larger than 2 cm (20·8%-28%) shows that VRT is a risky procedure for tumors with this feature. Several studies have shown that <1% of patients with early cervical cancer with favorable pathologic characteristics have parametrial involvement. There are only a few case reports about less radical procedures, such as conisation or simple trachelectomy with or without lymphadenectomy in cervical cancers < 2 cm of tumor diameter.

4. Over 2 cm of tumor diameter a few studies with different surgical radicality showed their results after neoadjuvant chemotherapy. The drawback of all studies in literatures is the small sample size and the relatively short follow-up. Neoadjuvant chemotherapy in fertility sparing surgery is an experimental concept, which requires verification in the future, especially concerning oncological findings.

5. Our goal was to find a surgical method to be used in patients with bulky tumors with an acceptable oncological outcome. Höckel et al [82] demonstrated that the most probable cause of the cervical cancer recurrence was incomplete removal of ligamentous mesometrium adjacent to the mesorectum. We presumed that survival of

surgically treated patients with cervical cancer might be improved by stringent complete removal of the parametria. Between November 1993 and November 2005, radical hysterectomy (RH) was performed in 563 consecutive patients with stage IB cervical cancer at St. Stephen Hospital. According to our treatment protocol, 492 (87.4%) of the 563 patients did not receive any adjuvant treatment. Five-year overall survival of 492 patients with stage IB cervical cancer treated with radical hysterectomy without adjuvant therapy was 94.0%.

6. Our surgical technique during the ART procedure, with regards to the extent of clearance of the tumor cell containing pelvic connective tissue, is identical to RH. Our hypothesis was that oncology safety of patients diagnosed with tumours >2cm in diameter and treated by ART would be similar to cases managed by RH. Between January 1999 and October 2006, a total of 36 patients with cervical carcinoma FIGO stage IB1-IB2 measuring greater than 2cm in diameter were explored with the intent of a fertility sparing ART and pelvic lymphadenectomy. 22 patients were eligible for ART procedure based on our exclusion criteria. Mean 5-year overall survival of ART patients over 2 cm of tumor was 95%. Out of the 22 patients, eight wished to fall pregnant. Four pregnancies were recorded in three patients. One pregnancy resulted in a first trimester miscarriage. Three pregnancies led to delivery of a healthy neonate, one at 28 weeks gestation and two at term. Although still preliminary, our results are encouraging and indicate that even tumours > 4cm may be successfully treated with ART.

Objectives and findings of the present study

Objectives of introducing ART (subject of the present study):

1. Fertility preservation in FIGO IA2 and IB cervical cancer patients – Initial steps and VRT
2. The development of a surgical technique, that can be adopted by gynecologic oncologists without a special training in vaginal radical approaches. ART
3. Study the oncological outcome, pregnancy outcome and quality of life consequences
4. Study the fertility preserving treatment options in cervical cancer patients under 2 cm of tumor diameter
5. Study surgical treatment of cervical cancer patients in FIGO I/B stadium without adjuvant therapy
6. Study the feasibility of the fertility preserving operation in terms of oncological outcome in cases where the tumor diameter is above 2 cm.

Findings of the present study:

1. VRT is a safe option in fertility preservation, but it needs a special training in a surgical technique with limited excess for trainees to the small operative field.
2. Radical abdominal trachelectomy is a technically feasible operation in adult and pediatric patients. ART has been developed and introduced in the every-days practice of gynecologic oncology throughout the world without demand of a special training.
3. ART is a safe method in terms of oncological outcomes. Long term quality of life consequences are better compared to radical hysterectomy. Pregnancy rate: most women (74%) attempting pregnancy after ART are able to achieve pregnancy and most of them deliver in the third trimester (52%).
4. VRT and ART seems to be oncologically safe method in patients with < 2 cm of tumor diameter. No clinical study has compared the two techniques so far. Less

radical treatment methods are under investigation. VRT is not recommended in cervical cancer treatment > 2 cm of tumor diameter.

5. A well-defined extension of the radical hysterectomy with clear anatomic borders and extensive removal of the pelvic connective tissue compartments seems to be an advantageous alternative of traditional (less extensive surgery combined with adjuvant radiotherapy) treatment for most patients with stage IB cervical cancer.
6. Oncological outcome of ART operated patients have been found identical to cases, treated by traditional methods. This technique seems to provide good oncological safety in cases, where the tumor diameter is above 2 cm.

1. Introduction

1.1. Cervical cancer

Cervical cancer is the second most common cancer in women in lower income, developing countries and the seventh most common cancer in countries with high GDP. More than 500 000 new invasive cervical cancer cases are estimated to be diagnosed worldwide every year.[1] The precise number of diagnosed cancer cases and the age distribution are unknown, because not all countries have complete cancer registration. In developed countries with a good public health infrastructure, screening of cervical cancer has led to an impressive reduction in incidence and mortality.

The major histologic types of invasive cervical carcinomas are squamosus cell carcinomas and adenocarcinomas. Squamosus cell carcinomas comprise 80% of cases, and adenocarcinoma and adenosquamous carcinoma comprise approximately 15 %. Even though the major histological type is squamous cell carcinoma, the ratio of adenocarcinomas increased to two folds in the past 20 years.

The staging of cervical cancer regarding the FIGO staging system is based upon the clinical finding. The staging system for cervical cancer was initiated by FIGO 1979. The current form of the staging system was adopted by the FIGO in 2009 after many revisions has been widely utilized throughout the world (Table 1.) .

Most patients in higher income countries who are diagnosed in the early stages of the disease have a good chance for being cured. However, both traditional treatment alternatives in early stage diseases (radical surgery and radiotherapy) destroy the fertility, and consequently both methods can lead to psychosexual dysfunction and a decreased quality of life (infertility increases the frequency of depression, stress, and sexual dysfunction.[2,3)] The mean age of women planning pregnancy in higher income societies has increased. Postponement of childbearing coupled with the comparatively young age at which many women are diagnosed with cervical cancer. [4] It's estimated that nearly 50% of all patients eligible for surgical management[5] are younger than 40 years of age.

Partial radical organ resection has become the optimum treatment of choice in many solid tumors, such as partial gastrectomy, nephrectomy, pneumonectomy, and colectomy to treat

malignancies affecting these organs.[6,7] In gynecologic oncology surgery, partial organ resection are relatively new techniques utilized in women with early cervical cancer who wish to retain fertility[8].

Table 1. : **FIGO stage of cervical carcinoma 2009.**

Stage I

Carcinoma strictly confined to the cervix; extension to the uterine corpus should be disregarded. The diagnosis of both Stages IA1 and IA2 should be based on microscopic examination of removed tissue, preferably a cone, which must include the entire lesion.

IA: Invasive cancer identified only microscopically. Invasion is limited to measured stromal invasion with a maximum depth of 5 mm and no wider than 7 mm.

IA1: Measured invasion of the stroma no greater than 3 mm in depth and no wider than 7 mm in diameter.
IA2: Measured invasion of stroma greater than 3 mm but no greater than 5 mm in depth and no wider than 7 mm in diameter.

IB: Clinical lesions confined to the cervix or preclinical lesions greater than Stage IA. All gross lesions even with superficial invasion are Stage IB cancers.

IB1: Clinical lesions no greater than 4 cm in size.
IB2: Clinical lesions greater than 4 cm in size.

Stage II

Carcinoma that extends beyond the cervix, but does not extend into the pelvic wall. The carcinoma involves the vagina, but not as far as the lower third.

IIA: No obvious parametrial involvement. Involvement of up to the upper two-thirds of the vagina.

IIA1: Clinical lesions no greater than 4 cm in size.
IIA2: Clinical lesions greater than 4 cm in size

IIB: Obvious parametrial involvement, but not into the pelvic sidewall.

Stage III

Carcinoma that has extended into the pelvic sidewall. On rectal examination, there is no cancer-free space between the tumour and the pelvic sidewall. The tumour involves the lower third of the vagina. All cases with hydronephrosis or a non-functioning kidney.

IIIA: No extension into the pelvic sidewall but involvement of the lower third of the vagina.

IIIB: Extension into the pelvic sidewall or hydronephrosis or non-functioning kidney.

Stage IV

Carcinoma that has extended beyond the true pelvis or has clinically involved the mucosa of the bladder and/or rectum.

IVA: Spread of the tumour into adjacent pelvic organs.

IVB: Spread to distant organs.

1.2. The classical surgical treatment of cervical cancer.

The classical surgical management of early-stage cervical carcinoma requires the extirpation of the uterus and cervix, along with radical resection of the parametrial tissues and upper vagina, together with complete bilateral pelvic lymphadenectomy (if pelvic lymph nodes positive some authors advocate periaortic lymphadenectomy as well).

It was Pare in the 16th century who first proposed the amputation of a cervical carcinoma as a treatment option. However, at this time surgery resulted a high mortality and even in the 19th century when Freund proposed and performed radical surgery for the management of cervical cancer, mortality rates of the procedure was still unacceptably high. [9]

The birth of the 20th century saw advances being made in surgical specialities with the introduction of safer anaesthetics, better antiseptics and later antibiotics. Surgeons such as Clark [10] in America and Wertheim [11] in Austria were pioneering the use of radical surgery with the aim of curing cervical cancer. Schauta [12] was treating cervical cancer with radical vaginal surgery and Okabayashi [13] has developed his radical hysterectomy technique in Japan. At the same time, radiotherapy was developed following the discovery of radium by the Curies and its therapeutic application by Abbe [14]. Many, even Wertheim himself, thought that radiotherapy would replace surgery for the treatment of cervical cancer. However, in the mid 20th century the radical hysterectomy and lymphadenectomy was reintroduced mainly through the work of Victor Bonney [15] in England and Joe Meigs [16] in America. In view of curative effectiveness and quality of life consequences radical surgery was demonstrated advantages over the radiotherapy, especially in young, early stage cohort of patients.

This operation yields 5-year survival rates of 75%-95%, in most reported series. Although the surgical principles of this operation were first described more than one hundred years ago, it has undergone only minor modification throughout the years and remains the basis for the surgical approach utilized by gynecologic oncologists today. [17-19]

1.3.Initial steps in preserving the fertility of cervical cancer patients.

The idea of preserving the uterine corpus and the adnexae during radical hysterectomy was first published by Aburel in 1932 and cited by Chiricuta in a Romanian textbook. This first conservative surgical approach was named ‘‘subfundic radical hysterectomy’’ by a Romanian gynecologist. No follow up data or successful pregnancies were reported .[20] In 1952 Novak presented a radical trachelectomy operation, which could be performed in women of reproductive age with cervical cancer in situ. Selected patients had to insist to be operated conservatively. He stated that this operation would be a radical extirpation of the cervix and upper part of the vagina, together the corresponding paracervical and paravaginal tissues .[21]

The first successful systematic conservative surgical approach for invasive cervical carcinoma was described and published by Dargent in 1994. This operation was referred to as radical vaginal trachelectomy and included a laparoscopic pelvic lymphadenectomy, which was followed by the removal of the cervix together with surrounding parametria in order to protect the corpus of the uterus and the ovaries.[22]

Concerns regarding the oncological safety of the method include the incomplete removal of the lateral parametria. Previous studies have demonstrated however, that parametrial metastases have a random pattern, thus partial resection of the parametria might hamper the oncological safety of the procedure. [23-24] By the use of the vaginal radical trachelectomy in larger tumours (>2 cm), recurrence rates as high as 29% have been reported. [25]

Smith J.R. et Ungar L. in 1997, reported their technique (abdominal radical trachelectomy) with the aim to preserve fertility of early stage cervical cancer cases without the oncological risk of incomplete parametrectomy. Abdominal radical trachelectomy has the potential to overcome some of these problems as the radicality (parametria resection) of the procedure can be identical to that of a traditional type III Wertheim hysterectomy. In the new technique the uterine cervix, complete parametria, and vaginal cuff were excised. A complete lymphadenectomy has been part of the ART procedure. The remaining uterine corpus was harvested (sutured) to the vagina [26-27.]

2. Fertility preservation techniques

2.1.Vaginal Radical Trachelectomy (VRT)

VRT consists of 2 main components; laparoscopic pelvic lymph node dissection and removal of the cervix up to the isthmus of the cervical canal, together with the surrounding parametrial and paracervical tissues via the vaginal route. This segment of the operation is similar to the Schauta's radical vaginal hysterectomy. A circumferential incision is made in the upper vagina, the rim of the vaginal mucosa is delineated, and a vaginal cuff is formed. Anterior and posterior vaginal mucosa are sutured to prevent tumor cell spillage (or closed with strong Chrobak forceps). Anteriorly, the supracervical ligament is cut and the bladder base is mobilized. Posteriorly, the Douglas pouch is opened then laterally, both pararectal spaces are entered. This maneuver delineates the recto- vaginal ligaments (inferior parts of the utero sacral ligament) that are divided using bipolar scissors. Similarly, both vesicovaginal ligaments (also called bladder pilars) have to be defined. For the purpose both paravesical spaces are entered laterally. At this point, the ureter has to be found out by palpating the bladder pillar on the retractor in- stalled in the paravesical space. The knee of the ureter is identified by palpation, and then the bladder pillars are separated from the cervix. When clearly identified by palpation, bladder pilar underneath the knee of the ureter can be divided. The bladder base is therefore completely detached from the cervico-isthmic part of the uterus which is maintained only by the lateral part of the cardinal ligaments. The arch of uterine artery is identified. Then a right angle forceps is passed through the paraisthmic window just underneath the uterine artery arch to define the upper limit of each cardinal ligaments. Checking again the position of ureters, clamps are placed on the proximal part of the cardinal ligament straight below the ureters and they are divided. Other clamps are placed perpendicularly to enable the selective ligature of the cervico vaginal arteries. Next, the proximal parametrium is resected after the re- identification of the ureters. The cervicovaginal branches of the uterine artery are selectively ligated while carefully avoiding damage to the uterine artery. The cervix is then amputated below the cervical isthmus and a trachelectomy specimen should be sent for a frozen section examination to ensure that the surgical margins are tumor-free. Endocervical surgical margins should be tumor-free at least 5-8 mm from the level of the tumor, and a 2 cm tumor-free vaginal cuff must be achieved, otherwise more of the endocervix should be removed, or a RH should be considered. Ideally, surgical margins

should be negative at least 1 cm beyond the tumor with 1 cm margins, including the paracervical tissues, and a vaginal cuff of at least 2 cm. If oncologically safe margins have to be obtained, a permanent cervico-isthmic cerclage is performed using a Prolene suture. Finally, the vaginal mucosa is reapproximate on closed to the new exocervix with interrupted sutures.[28,29]

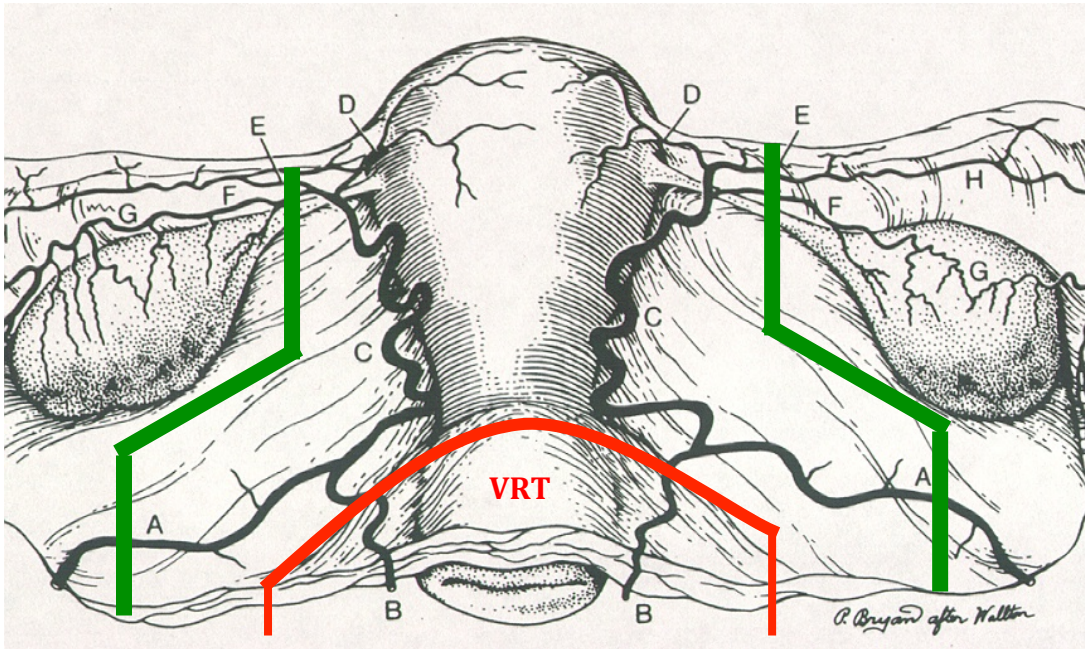
Oncological outcomes, such survivor and recurrence datas are the most important factors of such a relatively new technic. The vaginal approach – more than 600 cases of cervical cancer managed by VRT have been described in the literature - appeared to be oncologically safe in well selected patients with early stage disease and lesion size less than 2 cm based on the published articles. [30-34] Gien et al recently reviewed the literature on 600 cases and report an overall recurrance rate of 5,3 % and death rate of 3,4 %. The published datas showed, that the procedure is oncologically safe, but the recurrance rate is increased in tumor size over 2 cm. [33] The recommended inclusion criteries are seen in Table 2. Pregnancies after VRT were published by different centers. [30,35-37]

The explanation of the high recurrence rate over 2 cm tumor size could be the that VRT cervical specimen correlates to a Class II radical abdominal hysterectomy as described by Piver, Rutledge and Smith.[38] (Figure 1., Photo 1.) Incomplete removal of the lateral parametria where random metastases have been demonstrated histologically could be the reason of high failure rate in larger tumors.[39,40] In addition, learning the vaginal radical procedure can be difficult due to the limited access to the operative field for teaching and the low number of suitable candidates in individual centers.

Table 2.

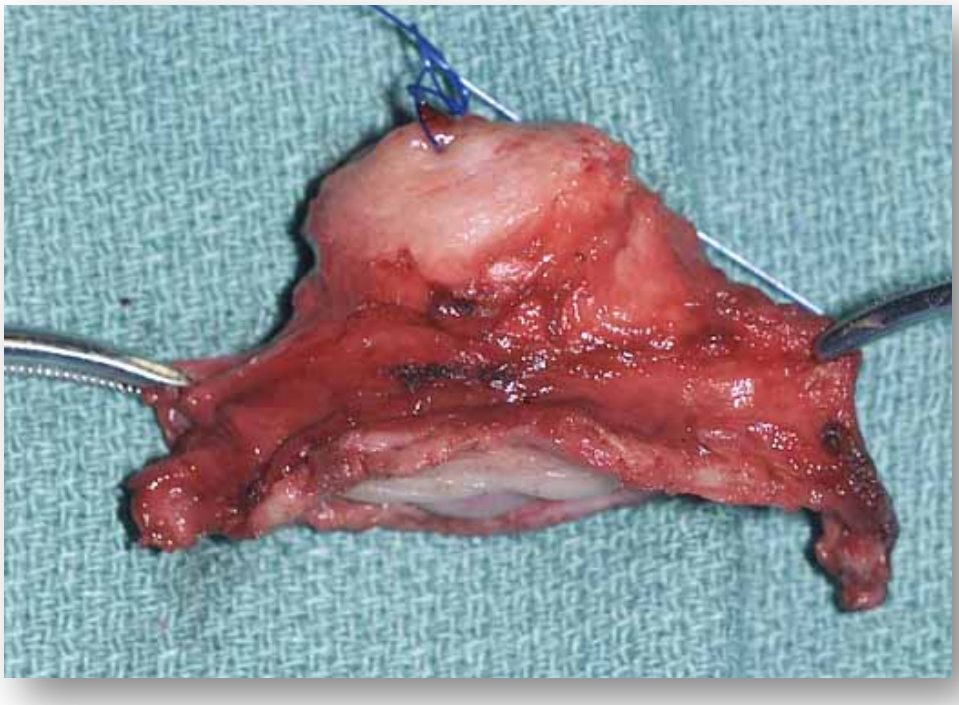
1. Strong fertility desire
2. Age <40 years
3. Proven diagnosis of invasive cervical cancer; ideally, disease located primarily on the ectocervix
4. Stage Ia1 with LVSI, Ia2, Ib1; Tumor size <2 cm
6. Limited endocervical involvement can be exactly determined by colposcopic examination and/or MRI;
7. No evidence of pelvic lymph node metastasis and/or other distant metastasis
8. Exclusion of unfavorable histology (e.g., neuroendocrine carcinoma)
9. Gynecologic oncologist who has an experience in laparoscopic and radical vaginal surgery

Figure 1.



Radical Hysterectomy Class III.

Photo 1.



2.2.Abdominal Radical Hysterectomy (ART)

As the first step of the ART procedure the peritoneum lateral and parallel to the infundibulopelvic ligament is opened, (round ligaments are preserved) and the pelvic retroperitoneal space is entered. A thorough pelvic lymphadenectomy, by removal of the complete fibro-fatty tissue content of the pelvic retroperitoneal space is completed from the levator any muscle level to the level of the bifurcation of the aorta is performed. The extent of the pelvic lymphadenectomy is identical to that in a traditional Piver type III radical hysterectomy, including the common iliac, superior gluteal, subaortic, presacral, external iliac and obturator nodes. The nodal tissue is analyzed by frozen pathological sections. If tumor is detected within the lymph nodes, the abdominal radical trachelectomy procedure is abandoned and the operation is converted to a laterally extended radical hysterectomy[41,42] and pelvic/ paraaortic lymphadenectomy or the patient is referred to chemo-radiotherapy.

The uterine vessels are ligated at their origins and the uterine corpus transected at the level of the internal os of the cervical canal. A cross section of the superior portion of the separated cervix is sent for frozen section to ensure a tumor-free margin towards the uterine corpus. The infundibulo-pelvic vessels, (which provide uterine perfusion), are mobilized and the uterine corpus retracted on them for the remaining parts of the operation (parametrectomy). The cervix is removed together with the parametria and the upper brim of the vagina, as in a conventional radical hysterectomy. (Figure 2., Photo 2.) Following a thorough dissection and removal of the cervix, parametria and upper vagina, the proximal vaginal margin is resutured to the seromuscular margin of the retained uterine body with a single layer running suture to re-establish continuity.

Figure 2.

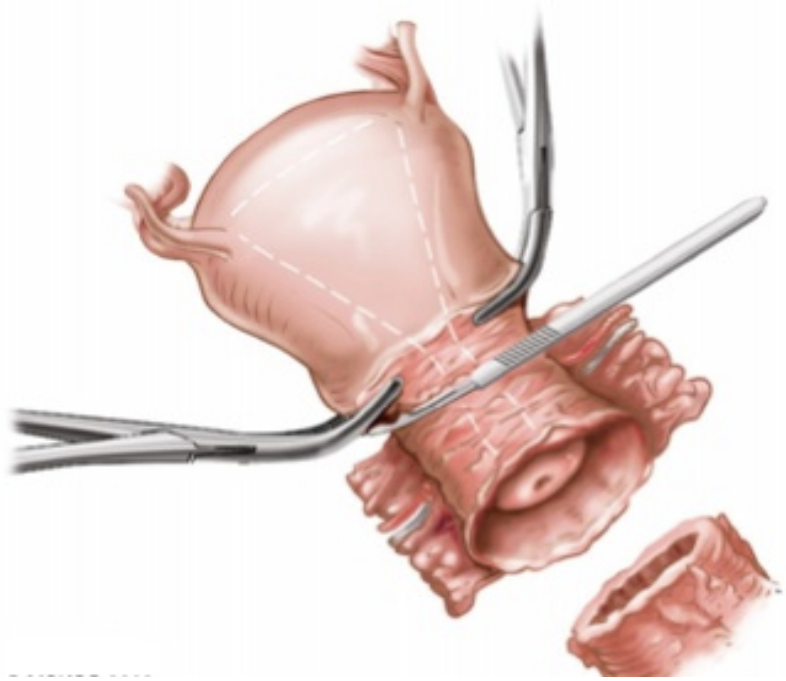
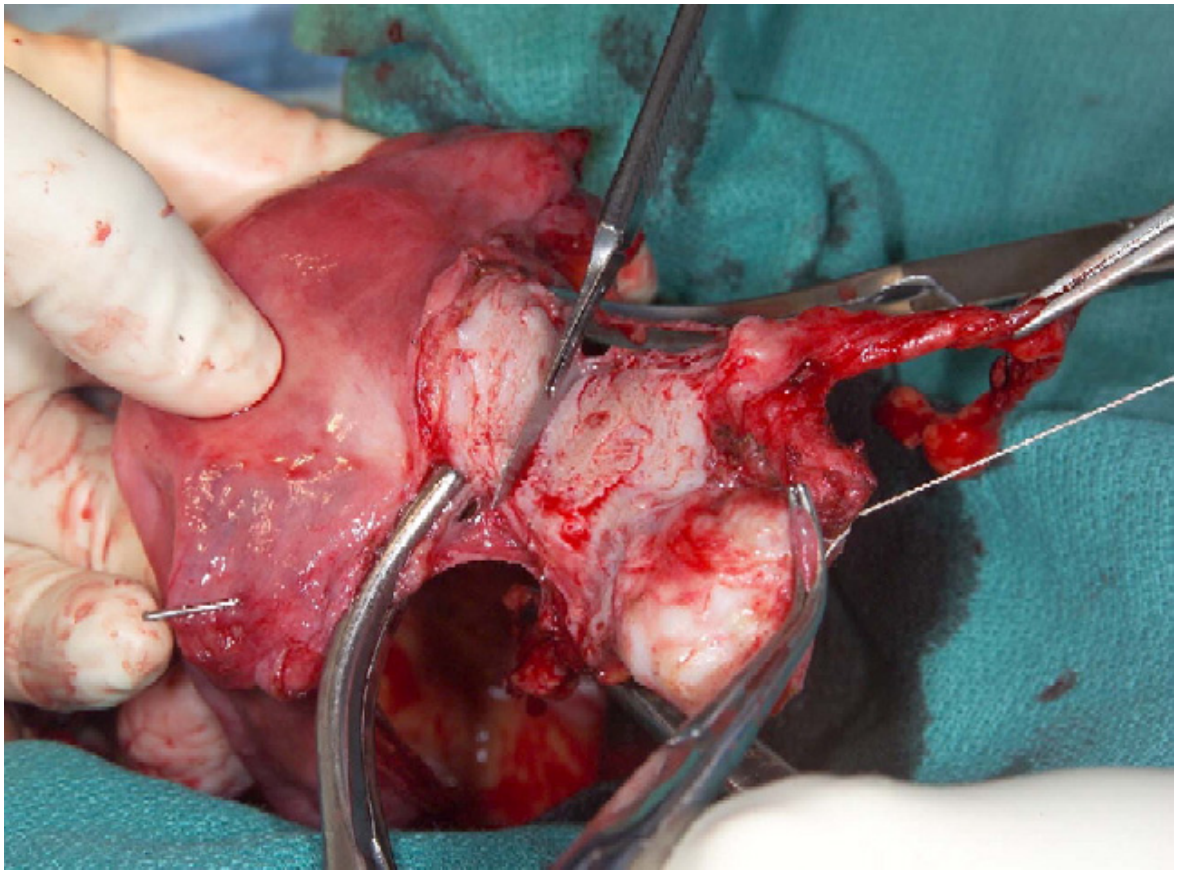
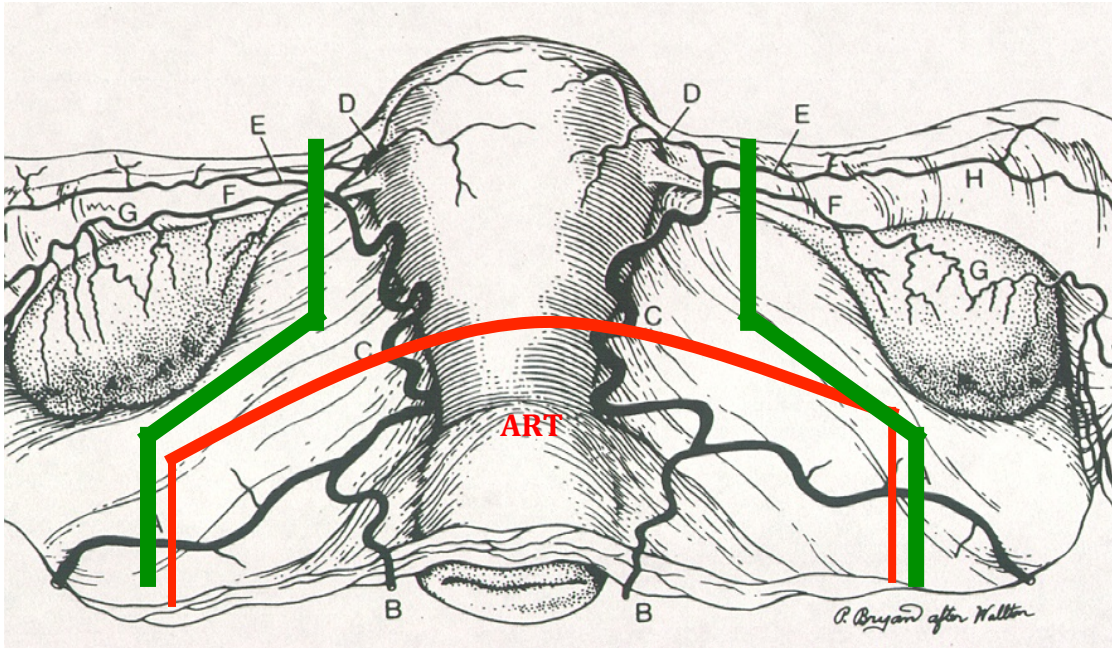


Photo 2.



Abdominal radical trachelectomy has the potential to overcome some concerns in regard to the VRT procedure. The radicality of the procedure can be identical to that of a traditional type III Wertheim hysterectomy. (Figure 3. , Photo 3.) The surgical-technical similarity of the abdominal radical trachelectomy and the traditional Wertheim procedure makes this technique easily adopted by surgeons having experience in radical hysterectomy. The number of RH procedures in high income countries have decreased, and fertility sparing surgery is applicable only for a small selected cohort of this shrinking group of cases. Considering these points of view, ART technique that does not need a special training for trained Wertheim surgeons seems to have an important advantage over VRT [43-45.]

Figure 3.



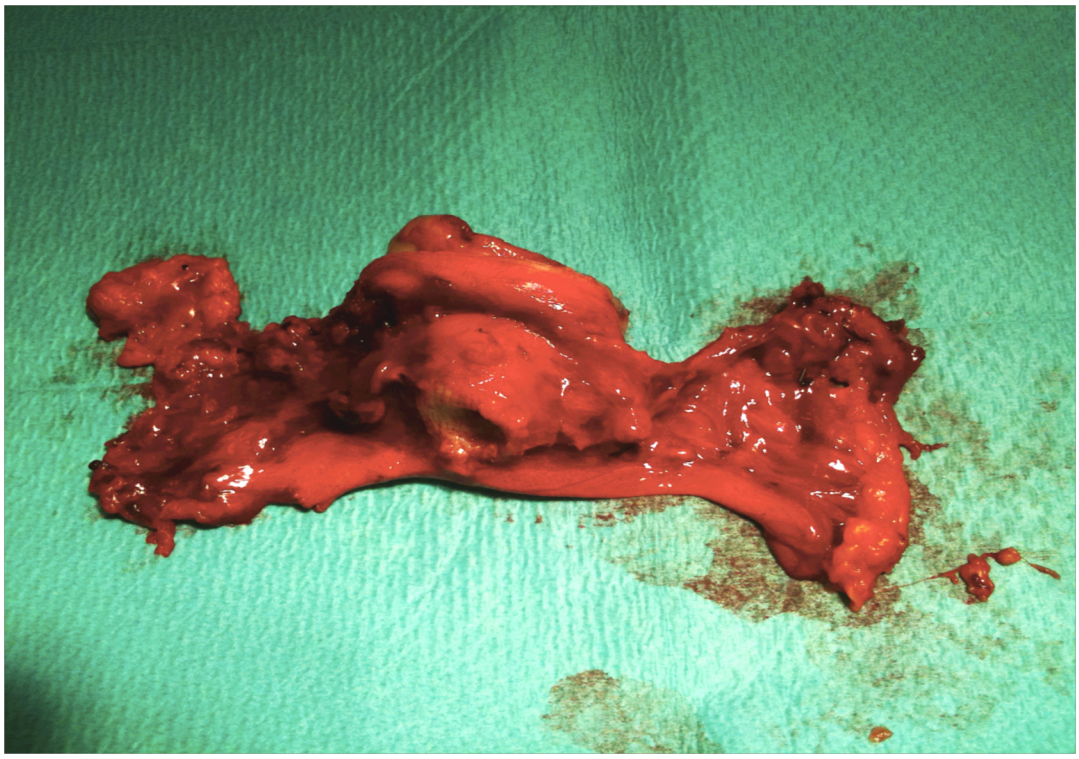
Radical Hysterectomy Class III.

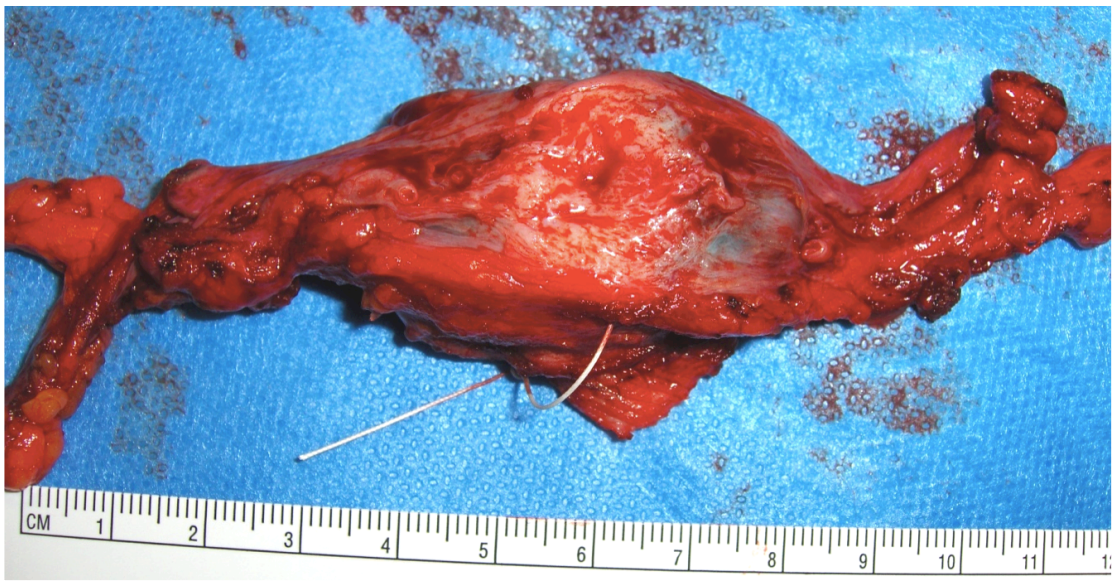
Our initial experience with the ART technique was published in 2005.[43] The 33 cervical cancer patients who expressed a desire for fertility-preserving surgery during the time period of 1997-2002 and underwent the procedure make up this prospective cohort, with follow up of all patients until October 2003. Three procedures were abandoned after positive pelvic nodes (two patients) and involvement of the margin between the amputated cervix and

the uterine fundus with tumor (one patient) were detected. The mean age of the remaining 30 patients was 30.5 years (range 23–37), mean weight 64.3 kg (range 50 – 85 kg); mean length of operating time 3 hours 46 minutes (range 2 hours 50 minutes to 5 hours) and mean number of lymph nodes removed from the pelvis 32.2 (range 17 – 44). Ten patients had FIGO stage IA2 tumors (9 squamous and 1 adenosquamous carcinoma), 15 had stage IB1 (14 squamous and 1 adenocarcinomas), while 5 women had stage IB2 tumors (3 squamous and 2 glassy cell carcinoma). Four of the stage IB1 tumors were over 2 cm in diameter. The largest tumor was 6 cm in diameter. One clinical stage IB1 tumor exhibited microscopic spread of tumor to the upper vagina. Lymphovascular space invasion was noted in 1 of 10 stage IA2, 3 of 15 stage IB1 and 4 of 5 stage IB2 tumors. Two of the tumors with lymphovascular space invasion also demonstrated perineural spread. Tumor-free margins of more than 5 mm were present in all cases. Patients with non-squamous tumors were advised of the risk of ovarian and distant metastases and all insisted on fertility-retaining surgery. No recurrences have been detected to date of publication, with a median follow up of 47 months (mean 32 months, range 14 – 75 months). A normal menstrual pattern resumed within eight weeks of surgery in all but two patients. In these two women, ultrasound examination was suggestive of obliteration of the endometrial cavity. Five of the 30 patients have tried to conceive resulting in two spontaneous and one IVF pregnancies. One pregnancy ended in miscarriage at five weeks estimated gestational age. Two patients delivered healthy babies at term by caesarean section with no complications. The babies weights were 3200 and 3350 g despite the reliance on the ovarian vessels for uterine perfusion.

Recently published datas of 3 institutions where patients planned for ART from 1999 to 2011. 101 patients were planned to retain the fertility, 70 of 101 women who had neither hysterectomy nor adjuvant therapy, 38 (54%) attempted pregnancy and 28 (74%) achieved pregnancy. Thirty-one pregnancies resulted in 16 (52%) third trimester deliveries. Six patients are currently pregnant with outcomes pending. Preservation of the uterine vasculature is not necessary for fertility; obstetrical outcomes are similar to those of the historical vaginal radical trachelectomy cohorts. [96]

Photo 3.





2.3.Radical Trachelectomy (RT) procedure with different technics

2.3.1.Laparoscopic Radical Trachelectomy

A laparoscopic alternative to the abdominal approach was developed for the use in centres where laparoscopic radical hysterectomy is a routine surgical treatment of early stage cervical cancer. The first laparoscopic abdominal radical trachelectomy was performed by Lee and colleagues. [46] Since that time, other investigators (including our team) have published their experience with this approach.[47-50]

The technic is the following [47] :

A 10-mm trocar was inserted supra-umbilically and two 5-mm trocars laterally to the umbilicus and lateral to the inferior epigastric vessels in each side. The surgery started with dissection of pelvic retroperitoneal space. Systematic pelvic lymphadenectomy followed to the level of aorta bifurcation. Lymphatic tissue was sent for intraoperative histology. Negativity of pelvic nodes was considered essential condition for continuation in procedure.

Ascendant branches of uterine vessels were cut at the level of the internal os and uterine corpus was separated from the cervix. Mobile uterine corpus connected to blood supply by the infundibulopelvic ligament and the round ligaments only was easily moved aside the operation field. An upper 5 mm slice of the resected cervix was cut and sent to frozen section to prove clean margins. The cervix was manipulated by 10 mm sharp grasper and a standard radical procedure continued. Paravesical and pararectal spaces were developed to the level of levator muscle fascia using dissecting forceps, uterine arteries were coagulated and cut at the level of hypogastric artery, lateral parametria were carefully transsected at the pelvic side wall using haemoclips, harmonic scalpel and scissors. Rectovaginal space was entered and bluntly developed, bladder peritoneum was opened and bladder dissected from the upper part of vagina, and ureter was completely freed from parametria. Bladder was sharply dissected from lateral parametria exposing bladder pillars, which were coagulated and resected at the posterior wall of the bladder. Posterior parametria were coagulated and transected from the sacrum to the level of final vaginal resection margins. Vagina was packed with two surgical gloves to prevent gas leakage. Finally, vagina was circularly cut by unipolar hook and cervix with vaginal cuff removed vaginally. Seromuscular edge of resected uterine corpus was fixed

to proximal vaginal vault with continuous running suture.

2.3.2. Robot-assisted laparoscopic fertility sparing Radical Trachelectomy

The da Vinci system provides instruments with a wrist function at the tip, movement downgrading, tremor elimination, a stable 3-dimensional view and an ergonomic working position. These features may help the surgeon overcome some of the limitations associated with traditional laparoscopic surgery. The first robot-assisted trachelectomy was performed in 2007.[51] The technique is new and only 37 cases have been published in English literature to date. Reproducibility and accuracy have been studied and compared to the vaginal approach. It demonstrated that for robot-assisted trachelectomy the length of the remaining cervix was equally accurate as for the vaginal approach, the length of the parametria removed was longer.[45] Standardized technic of the procedure is not written here, because only a few studies were published until now. [51-54]

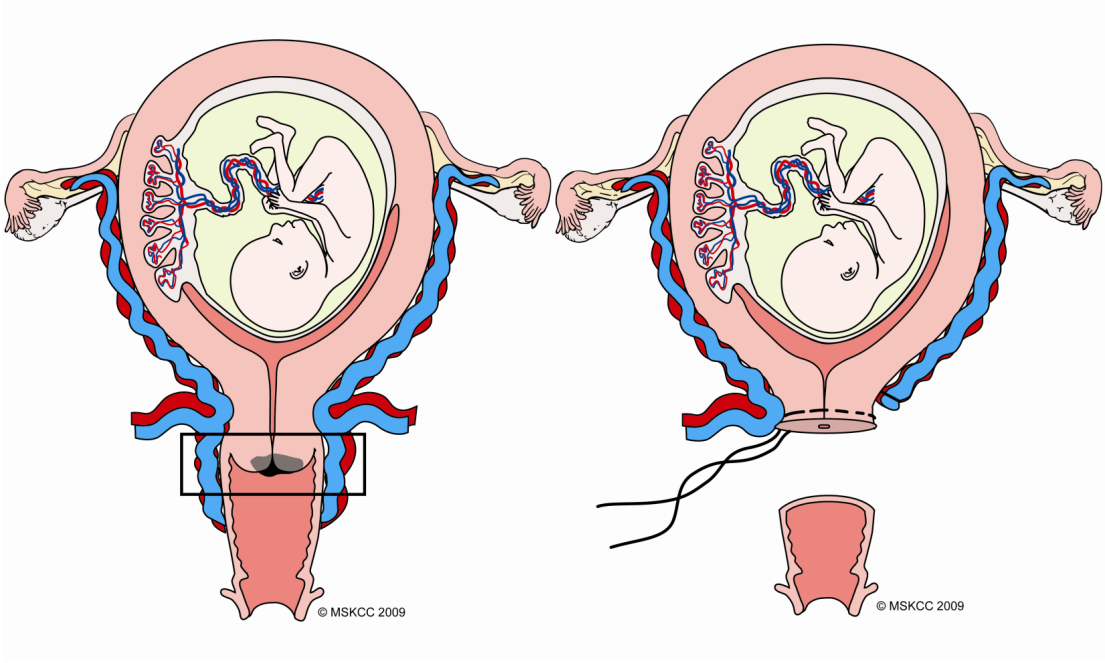
2.4. Special indications for ART procedure

2.4.1.Gestation and early cervical cancer

The occurrence of malignancies during pregnancy has increased over the last decades**.** They complicate approximately 1 per 1000 pregnancies. There is almost always a conflict between optimal maternal therapy and fetal well-being, since either maternal or fetal health, or both, will be compromised. Treatment delay for the sake of the maturation of the fetus is the generally adopted policy in cases where cervical cancer is diagnosed during the 2nd half of the pregnancy**.** In cases of invasive cervical cancer diagnosed in the first trimester of a pregnancy, treatment delay - necessary to secure the health chances of the fetus - would

impose an undue maternal risk. Treatment of the mother without delay, that immolates the fetus, has become the general policy of treatment. Besides, the incidence of cervical cancer is increasing in young women at a time when they are delaying their childbearing.

Abdominal trachelectomy has been reported by our team[56] as a potential option in patients who have strong desire to attempt preservation of pregnancy, fertility and treat the cancer diagnosed in the first trimester of pregnancy without delay. Our first experience was followed in other institutions by advances in fertility-sparing surgery for stage IB1-2 cervical cancer lead to the successful utilization of radical abdominal trachelectomy during the early second trimester of pregnancy. This approach in early gestation is feasible and resulted in a favorable oncologic and obstetrical outcome. From technical standpoint it appears that unilateral uterine vasculature perfusion is sufficient in our successful cases reported to carry the pregnancy to term without evidence of fetal growth restriction. Unlike other treatments (radical hysterectomy, radio-chemotherapy) ART did not result pregnancy terminations. Radical trachelectomy may provide a unique option for first trimester pregnant women with stage IB1 and 2 cervical cancer who have a strong desire to avoid definitive pregnancy termination and commence treatment without delay.[55-56]



2.4.2. Pediatric ART for tumors arising in site of the cervix

A 14-year-old girl who was discovered to have a large solitary fibrous tumor of the uterine cervix, an unusual site for these tumors, to highlight the diagnosis and management if these tumors. Complete resection was achieved by means of a fertility sparing ART.[57] Solitary fibrous tumor (SFT)are rare mesenchymal tumors arising in the pleura, mediastinum, pericardium, lung parenchyma, parotid, abdominal and pelvic organs.[58] Complete resection with a clear surgical margin is usually a curative treatment for these tumors. Local recurrence or metastasis, usually to bone, lung or liver is thought occur in 10-15 % of SFTs but has been described in up to a third of tumors in reported series. Lymph node metastasis appears to be rare; in one large series, lymph node metastasis was reported in 6 of 223 cases (3 %).[59] Due to the generally excellent clinical outcome with complete surgical resection there are no systematic trials of chemotherapy or radiotherapy in these patients.[58,60] Two additional reports were published by the same group about embryonal rhabdomyomsarcoma and cervical clear cell carcinoma arising in the cervix.[61,62]

3. Fertility preserving in different prognostic groups of patients

3.1 Fertility preserving at patients with less than 2 cm of tumor diameter

3.1.1. ART and VRT

Tumor size is an important criterion for fertility preservation surgery in most centers. If tumor stage I/A/1 without LVSI a simple conisation is considered an oncological safe method treating cervical cancer. Most international protocols (NCCN, ACOG) consider appropriate candidates for fertility sparing surgery patients with tumors of FIGO stage IA1 with lymphovascular space involvement (LVSI), IA2, and IB1. Most centers include stage IB1 tumors of less than 2 cm only. Oncology outcomes are reported acceptable if the tumor does not exceed 2 cm in diameter and if it does not infiltrate more than half of the cervical

stroma.[29,32,63] The 5-year survival rate is around 95% in these series. With the same treatment strategies (limited extent pelvic connective tissue removal) in IB1 tumors larger than 2 cm, the risk of recurrence following limited radicality procedures is significantly higher.[25] Expert colposcopy, high quality imaging and EUA is the standard examination before decision is reached about the feasibility of fertility sparing surgery, and one important parameter is the exocervical diameter.[63,64,65,66]

Beside the size of the tumor and the stromal invasion LVSI is the most commonly discussed risk factor.[67,68] LVSI was present in around a third of women who underwent fertility sparing surgery in a number of materials.[69,48,38] Most centers consider these risk factors, and regard the combinations of the prognostic parameters as potential exclusion criteria.

VRT and ART are generally considered oncologically safe under the limit of 2 cm tumor size. In more than 10% of reported cases, VRT was done in tumors larger than 2 cm. A comparison of recurrences in tumors less than 2 cm in size (12 recurrences in 409 women [2·9%]) with recurrences in tumors larger than 2 cm (11 recurrences in 53 women [20·8%-28%]) shows that VRT is a risky procedure for tumors larger than 2 cm.[29,32,38]

Characteristics, oncological outcome, and pregnancy outcome of VRT and ART in Table 4 and 5.

Table 4.

	Shepherd[22,23]	Sonoda[24]	Pahisa[28]	Chen[29]	Hertel[30]	Dargent[32,33]	Plante[10,11,33]	Covens[34-36]	Burnett[16,17]	Schlaerth[38]
Period	1994-05 1994-07	2001-06	2000-07	2000-04	1995-2005	1986-2003	1991-2003 1991-2008	1999-2003 1999-2007	1995-2001	1995-99
Planned VRT, n	158	43	15	16	108	135	82	93	21	12
Fertilities spared, n	138	36	13	16	106	118	72	91	18	10
N1, n	7/123	2	0	0	4	9	4	2	1	0
LVSI, n	49/158	NA	1/15	1/16	38/108	43/118	14/72	31/93	6/21	1/10
Mean age (range), years	30·6 (21–45)	31 (20–40)	NA	27·6 (24–31)	32 (21–41)	NA	31 (21–42)	30 (NA)	30 (23–41)	30·9 (22–44)
Nulliparous women, n	97/123	35/43	NA	14/16	92/108	NA	54/72	NA	16/21	12/12
Histology, n										
SCC	103	24	9*	14	74	90*	42	40	12	4*
AC	51	16	6*	2	33	25*	27	50	9	5*
Other	4	3	0	0	1	3*	3	3	0	1*
Recurrence, n										
Size <2 cm	NA	1/36	1/11	0/9	3/105	1/91	1/64	5/83	NA	0/10
Size >2 cm	NA	0	1/2	0/7	1/1	6/27	2/8	1/8	NA	0
Deaths, n	4	1	1	0	2	5	2	4	1	0
Pregnant women, n	NA	11	3	5	18/106	33/118	51	18	3	4
Conceptions, n	88	11	3	5	17	56	90	22	3	4
First trimester loss, n	22	3	0	0	3†	14	23	3	0	0
Second trimester loss, n	12	0	0	2	0	8	3	3	1	2
Delivery, n										
Before week 32	10	0	0	0	3		4	3‡	0	0
Weeks 32–36		0	0	1	5§	5¶	9‡	3	0	1
Term	35+2§ || **	4	1	1	4	29	51	12	2	1
Ongoing pregnancy	7	4	2	1	3	NA	NA	NA	NA	NA

VRT=vaginal radical trachelectomy. N1=positive lymph nodes. LVSI=lymphovascular space involvement. NA=not available. SCC=squamous-cell carcinoma. AC=adenocarcinoma. *Only patients after VRT. †Two abortions induced at patients' request. ‡Two twin pregnancies. §Twins. ¶These data are for before week 32 and weeks 32–36. ||Surrogate livebirth. **These data are for 32–36 weeks and term.

Table 5.

	Abu Rustum[35,40]	Pajera[41]	Duska[42]	Nishio[43]	Cibula[44]	Ungar[45,46]
Period	2005–08	2002–08	1999–2007	2002–08	2001–08	1997–2002
Planned ART, n	22	15	10	71	24	33‡
Fertilities spared, n	15	14	10	61	17*	30§
N1, n	6	1	0	15	4	2
LVSI, n	9	5	NA	31	2	8
Mean age (range), years	33 (23–43)	30 (25–38)	31·7 (25–38)	33 (26–44)	32·4 (23–37)	30·5 (23–37)
Nulliparous women, n	20	NA	9	NA	21	NA
Histology, n						
SCC	9	11	3	58†	14	26†
AC	13	4	7	2†	10	1†
Other	0	0	0	1†	0	3†
Recurrence, n						
Size <2 cm	NA	0	0	1/48	1/14	0/21
Size >2 cm	NA	0	0	5/13	0/3	0/9
Deaths, n	0	0	0	NA	NA	0
Pregnant women, n	2	3	2	4	6	13
Conceptions, n	2	3	4	4	6	13
First trimester loss, n	1	0	1	0	1	4
Second trimester loss, n	0	0	0	0	0	0
Delivery, n						
Before week 32	0	1	0	2	2	0
Weeks 32–36	0	0	1	0	0	1
Term	0	2	1	2	3	5
Ongoing pregnancy	1	0	1	0	0	3

81 fertilities spared. ART=abdominal radical trachelectomy. N1=positive lymph nodes. LVSI=lymphovascular space involvement. NA=not available. SCC=squamous-cell carcinoma. AC=adenocarcinoma. *Three were done completely laparoscopically. †Only patients after ART. ‡Updated data; 91 Planned ART. §Updated data.

3.1.2. Less radical technics

Several studies have shown that <1% of patients with early cervical cancer with favorable pathologic characteristics have parametrial involvement. [71-74] In addition, it has been shown that in approximately 60% of patients undergoing radical trachelectomy, the final pathologic specimen contains no residual disease.[29] Retrospective studies of parametrial involvement in small tumours with infiltration of less than 10 mm or less than half of the stroma, with negative pelvic lymph nodes, support less radical surgery without resection of paracervical tissue.[71-74] The minimum risk of parametrial involvement in cases of negative SLNs was confirmed by the first prospective study.[75]

There are only a few case reports about conisation or simple trachelectomy with or without lymphadenectomy in cervical cancers. A less radical surgical protocol was first published by Rob and colleagues.[63] This procedure is divided into two steps: first, laparoscopy, SLN identification and frozen section, and pelvic lymphadenectomy are done; second, conisation (stage IA1 with LVSI and stage IA2 tumors) or simple trachelectomy (stage IB1 tumors, less than 2 cm) are undertaken when the SLNs are negative. Updated findings were published in 2008.[70] Of the 40 patients enrolled, 6 (15%) had positive sentinel lymph nodes on frozen section, and radical hysterectomy with pelvic lymphadenectomy was immediately performed. In the remaining patients, only a pelvic lymphadenectomy was performed. Following a 7-day interval to allow pathologic confirmation of negative lymph nodes, a large cone or simple vaginal trachelectomy was performed. With a mean follow-up of 47 months, one recurrence has been reported in a patient with a stage IB1 tumor with 8 mm of cervical stromal invasion and LVSI present. The patient was treated with chemoradiation and was reported to be without evidence of disease 62 months post-treatment.

Characteristics and oncological outcome of patients who underwent simple trachelectomy or large cone are seen in table 6.

Table 6.

	Characteristics
Period	1999–2006
Planned simple trachelectomy/cone, n	40
Fertilities spared, n	32
N1, n	6
Mean age (range)	28·3 (24–35)
Nulliparous women, n	25
Histology, n	
SCC	32
AC	7
Other	1
Stage, n	
IA1+LVSI	3
IA2	10
IB1	27
LVSI, n	17
Recurrences, n	1/32
Deaths, n	0

N1=positive lymph nodes. SCC=squamous-cell carcinoma. AC=adenocarcinoma. LVSI=lymphovascular space.

3.2.Fertility preserving at patients with more than 2 cm of tumor diameter

3.2.1.Neoadjuvant chemotherapy

One of the limitations of fertility preserving surgery is deep stromal invasion and tumors larger than 2 cm. VRT in tumors larger than 2 cm shows high recurrence rate, hence it's a risky procedure in these special cohort of patients and not recommended to perform. Some centers use neoadjuvant chemotherapy in "bulky" cervical cancers with the aim of downstaging before radical hysterectomy. [76,77] Currently, three approaches have been published on neoadjuvant chemotherapy and fertility sparing surgery. First, Maneo and colleagues used neoadjuvant chemotherapy before fertility sparing surgery (conisation). [78] 21 women with tumors 10–30 mm in size (12 patients > 2 cm of tumor diameter) were included in this protocol. In 16 of these women, fertility was preserved. Minimum (less than 3

mm) or no residuum was found in 17 women, and none of the patients' tumors progressed on chemotherapy. Initially, lymphadenectomies were done by laparotomy, and then laparoscopically. Two women had positive lymph nodes. No recurrences were noted, but three women had precancerous lesions during follow-up.

Plante and colleagues reported on three women who had neoadjuvant chemotherapy.[79] The protocol of chemotherapy was the same as in the study by Maneo and colleague and only tumors between 3 and 4 cm were included. Surgery consisted of laparoscopic pelvic lymphadenectomy, with identification of SLNs, and VRT. Complete histopathological remission was achieved in all cases. In August 2009, all the patients were without evidence of disease; one patient delivered one baby and one patient delivered two (table 7).

The third approach is known as the Prague protocol.[80] Women with tumors larger than 2 cm, but which had not infiltrated more than two thirds of the stroma, were included. High dose density neoadjuvant chemotherapy was used: three cycles of chemotherapy at an interval of ten days. Fertility was preserved (simple trachelectomy) in seven of nine women. One woman opted for a radical hysterectomy after chemotherapy. Positive endocervical margins were present in another patient. Complete remission or minimal residuum of less than 2 mm was diagnosed in seven patients (table 7). One recurrence in the ovary was diagnosed 6 weeks after spontaneous delivery. This woman died of haematogenous dissemination of the tumor. Five women became pregnant.

Table 7. Characteristics, oncological outcome, and pregnancy outcome after neoadjuvant chemotherapy and fertility sparing surgery

	Robova[15] and Rob[50]	Plante[14]	Maneo[16]
Period	2005–07	2004–05	1995–2007
Chemotherapy	Cisplatin 75 mg/m² plus ifosfamide 2 g/m² every 10 days; or cisplatin 75 mg/m² plus doxorubicin 35 mg/m² every 10 days	TIP; or TEP every 21 days	TIP or TEP
Planned surgery, n	9	3	21
Fertility spared, n	7	3	16
N1, n	0	0	2
Mean age (range), years	29·3 (24–33)	32·3 (26–36)	30 (17–39)
Nulliparous women, n	8	2	NA
Histology, n			
SCC	7	3	9
AC	2	0	12
Others	0	0	0
Tumour size, n			
<2 cm	0	0	9
>2 cm	9	3	12
LVSI, n	9	NA	1
Recurrences, n	1/7*	0	0/16
Pregnant women, n	5/7	2	6/16
Conceptions, n	5	3	10
1st trimester loss, n	0	0	1
2nd trimester loss, n	0	0	0
Delivery, n			
Before week 32	1	0	2
Weeks 32–36	0	1	0
Term	3	2	7
Ongoing pregnancy, n	1	NA	NA

N1=positive lymph nodes. NA=not applicable. SCC=squamous-cell carcinoma. AC=adenocarcinoma. LVSI=lymphovascular space invasion. TIP=paclitaxel 175 mg/m² plus cisplatin 75 mg/m² plus ifosfamide 5g/m². TEP=paclitaxel 175 mg/m² plus cisplatin 75 mg/m² plus epirubicin 80 mg/m². *Unpublished case.

In the latest report by Köhler et al [81] 18 cervical cancer patients with stage IB1 ≥ 2 cm in diameter or stage IB-2 recruited wishing to preserve fertility were offered the opportunity to be treated with neoadjuvant chemotherapy if prior laparoscopic pelvic and paraaortic lymphadenectomy showed no metastasis. In 67% of these women tumor positive lymph nodes were detected and therefore they received chemoradiation therapy. After a mean follow-up of 25.2 months nine patients are without disease and three recurred and deceased. Six women (33%) received NACT in a three weekly scheme, afterwards VRT was performed. No

relapses were observed in the group of women receiving NACT and RVT (follow up in this group 30.6 months [range: 8–70]).

All the above-mentioned studies were different in terms of the surgical radicality used after neoadjuvant chemotherapy. The drawback of all studies in literatures is the small sample size and the relatively short follow-up. Neoadjuvant chemotherapy in fertility sparing surgery is an experimental concept, which requires verification in the future, especially concerning oncological findings.

3.2.2. Radical hysterectomy in patients with tumor over 2 cm.

Our goal was to find a surgical method to be used in patients with bulky tumors with an acceptable oncological outcome. It has been several times demonstrated, that the location of parametrial metastases in surgical specimens being randomly distributed with an equal number of metastatic foci in the lateral and medial parametria.[39] Detailed analysis of pelvic relapse probability maps accomplished by Höckel et al [82] demonstrated that the most probable cause of the cervical cancer recurrence was incomplete removal of ligamentous mesometrium adjacent to the mesorectum, from the central lower to the peripheral upper parts. This is acceptable explanation for the failure of VRT procedure in tumors over 2 cm. Abdominal radical trachelectomy has the potential to overcome this problem as the radicality of the procedure can be identical to that of a traditional type III Wertheim hysterectomy.

Nonrandomized retrospective studies demonstrated that adjuvant radiotherapy after radical hysterectomy decreased the risk of pelvic recurrence but did not improve the overall survival in high and intermediate-risk cervical cancer.[83] Based on these data, we presumed that survival of surgically treated patients with cervical cancer might be improved by stringent complete removal of the parametria, which contains lymphatic nodes and vessels.

Our experience with surgically treated I/B/1-I/B/2 patients with cervical cancer

In 1993, a well-defined extension of the radical hysterectomy with clear anatomic borders was stipulated and adopted by all gynecologic cancer surgeons at St. Stephen Hospital. Laterally extended parametrectomy (LEP) was adopted as standard treatment policy in cases of positive pelvic nodes proven by intraoperative histology.[41]

Between November 1993 and November 2005, radical hysterectomy was performed in 563 consecutive patients with stage IB cervical cancer at St. Stephen Hospital. We stipulated conditions indicative for adjuvant treatment as follows: disease spread beyond the anatomical borders of the excision (positive surgical margins and tumor spread to the ureter channel) or specific tumor spread direction (tumor breakthrough of the lymph node capsule, occult para-aortic lymph node metastasis, and tumor spread to the uterine corpus). We consider these criteria to indicate poor prognosis, unlikely to be influenced by a more extensive parametrectomy.

Clinical characteristics were collected from medical records. Overall survival data were obtained from the National Population registry and the National Health Care registry (every citizen of the Hungarian Republic is covered by the National Health Scheme, and oncological treatment is not possible outside NHS hospitals), which provide these data for every patient without anyone lost for follow-up. The living patients were followed up for 64 to 145 months.

Results

The mean operating time of 563 completed radical hysterectomies was 190 minutes (range, 90-360 minutes); the mean blood loss was 800 mL (range, 50-4000 mL). Blood transfusion (average of 3 units) during or after surgery was needed in 70.0% of cases. No treatment-related death occurred.

Forty-one patients (7.3%) had postoperative complications, which required surgical treatment.

In 71 patients (12.6%), we advised adjuvant radiotherapy or chemoradiotherapy. No adjuvant

treatment was purposed in 492 (87.4%) of 563 completed radical hysterectomy cases. Clinical characteristics of the whole cohort of 563 patients are presented in Table 8.

Variable	No. Adjuvant Neg. (%)	No. Adjuvant Pos. (%)
Age, yrs*	42 (22–60)	
Stage, n (%)		
IB1	324 (65.9)	10 (14)
IB2	168 (34.1)	61 (86)
Pathology stage more advanced than FIGO stage, n (%)	86 (17.5)	54 (76)
pIIA	46 (9.3)	9 (12.7)
pIIB	40 (8.2)	37 (52)
Occult distant met.	–	8 (11.3)
Histologic finding, n (%)		
Squamous cell carcinoma	402 (81.7)	60 (84.5
Adenocarcinoma	70 (14.2)	8 (11.2)
Clear cell carcinoma	17 (3.5)	1 (1.5)
Anaplastic cancer	1 (0.2)	2 (2.8)
Mucinous carcinoma	1 (0.2)	–
Carcinosarcoma	1 (0.2)	–
Lymph node metastases, n (%)	70 (14.2)	36 (50.7)
In stage IB1 (n = 324)	28 (8.6)	3 (30)
In stage IB2 (n = 168)	42 (25.0)	33 (54.1)
Lymphovascular space involvement, n (%)	109 (22.2)	51 (72)
Invasion >1/3 of the cervical stroma, n (%)	320 (65.0)	51 (72)
Two of 3 GOG 92/RTOG 87-06 intermediate risk criteria,†‡ n (%)	62 (12.6)	54 (76)

*Data are presented as median (range).
†GOG 92/RTOG 87-06 intermediate risk criteria[10]: tumor diameter greater than 4 cm, invasion greater than 1/3 of the cervical stroma, and lymphovascular space involvement.
‡These patients did not meet SWOG 8797/GOG 109/RTOG 9112 high-risk criteria[8]: stage pIB, lymph node negative, and R0.

Table 8.

According to our treatment protocol, 492 (87.4%) of the 563 patients did not receive any adjuvant treatment. The survival data are summarized in Table 9. Five-year overall survival of 492 patients with stage IB cervical cancer treated with radical hysterectomy without adjuvant therapy was 94.0%. Five-year overall survival in stage IB1 disease was

96.0%; in stage IB2, it was 87.0%. The number of dissected lymph nodes identified by pathologic examination ranged between 30 and 55. Pathological stage, histologic classification, lymph node metastases, lymphovascular space involvement, and perineural spread did not seem to influence the prognosis. Sixty-two patients (12.6%) had intermediate-risk disease defined by GOG 92/RTOG 87-06 [84] (presence of any 2 of 3 criteria: tumor size >4 cm, lymphovascular space involvement, and invasion >1/3 of the cervical stroma). Five-year overall survival in this group was 88.0%. One hundred twenty-eight patients (26.0%) in our study had high-risk cervical cancer according to SWOG 8797/GOG 109/RTOG 911 criteria. Seventy of them were lymph node positive; the 5-year overall survival of these patients was 91.0%. Laterally extended parametrectomy procedure was performed in all lymph node-positive cases. The 5-year overall survival of the patients with lymph node-positive cervical cancer according to stage was as follows: stage IB1 (n = 26), 96.0%; stage IB2 (n = 16), 88.0%; pIIA (n = 12), 100.0%; and pIIB (n = 16), 81%. In 58 patients with lymph node-negative disease, the pathology stage was more advanced (stage pIIA or pIIB) than the International Federation of Gynecology and Obstetrics stage. The 5-year overall survival in this group was 88.0%. The 5-year overall survival of 190 patients (38.6%) at high and intermediate risk was 90.0%.

Adjuvant chemoradiotherapy was advised in 71 cases (12.6%), in which final pathologic finding revealed tumor spread beyond the study criteria.

94% overall survival was achieved with a completed 5-year follow-up as the result of a well-defined radical hysterectomy, which was used without adjuvant treatment in most of stage IB cervical cancer. This outcome is similar to the 96% 5-year overall survival after total mesometrial resection without adjuvant therapy reported by Höckel et al.[82] It enabled us to assume that complete removal of the fibro-fatty tissue content of the pelvis provides at least the same or even better survival than any reported traditional treatment modality (Table 10).[85-87.] Our aim was to define surgical borders of dissection irrespective of ligaments, lymph node groups, and surgical planes. In this respect, we neglected the anatomical definition of the removed tissue blocks and focused on structures left cleared from the overlying connective tissue. This surgical definition was possible to teach and learn; it was adoptable for all surgeons in our team.

A well-defined extension of the radical hysterectomy with clear anatomic borders and extensive removal of the pelvic connective tissue compartments seems to be an advantageous

alternative of traditional (less extensive surgery combined with adjuvant radiotherapy) treatment of most patients with stage IB cervical cancer.

Groups	5-Year Overall Survival, %
Surgery, no adjuvant treatment (n = 492)	94.0
Stage IB1 (n = 324)	96.0
Stage IB2 (n = 168)	87.0
Two of 3 GOG 92/RTOG 87-06 intermediate risk criteria*† (n = 62)	88.0
SWOG 8797/GOG 109/RTOG 9112 high-risk criteria (n = 128)	
Lymph node positive (n = 70)	91.0
pIB1 (n = 26)	96.0
pIB2 (n = 16)	88.0
pIIA (n = 12)	100.0
pIIB (n = 16)	81.0
Upstaging, lymph node negative (n = 58)	88.0
Intermediate risk + high risk (n = 190)	90.0

*GOG 92/RTOG 87-06 intermediate risk criteria[10]: tumor diameter greater than 4 cm, invasion greater than 1/3 of the cervical stroma, lymphovascular space involvement.

†These patients did not meet SWOG 8797/GOG 109/RTOG 9112 high-risk criteria[8]: stage pIB, lymph node negative, R0.

Table 9.

Study (Reference)	Year	Stage	5-Year Survival, %	
			Surgery	Surgery + Adjuvant Treatment
Landoni et al [11]	1997	IB–IIA	Overall, 84.0%; disease-free, 74.0%	Overall, 84.0%; disease-free, 74.0%
Landoni et al [12]	2001	IB–IIA	Overall, 77.0%; disease-free, 73.0% (for Piver III hysterectomy)	
Landoni et al [13]	2012	IB–IIA	Overall, 95.0% (for Piver III hysterectomy)	
Sedlis et al,[10] GOG 92/RTOG 87-06	1999	IB	Overall, 78.6%; recurrence-free, 72.1%	Overall, 86.9%; recurrence-free, 84.7%
Höckel et al[4]	2009	IB–IIB	Overall, 96.0%; disease-free, 94.0%	NA

NA, not assessed.

Table 10.

Conclusions of our study in relation to fertility preserving ART indications:

1. Extensiv and well defined radical pelvic connective tissue removal (cellulectomy) provide equal or better survival chances than any combinations of surgery and or chemo-radiotherapy for 90% of Stage IB cervical cancer patients.
2. Patients who are unfit for the surgery only treatment strategy (lymph node metastasis with tumor extending beyond the anatomy borders of the lymph node, paraaortic lymph node involvement, ureter channel involvement and tumor spread to the uterine corpus) are referrals for adjuvant treatment.
3. Our selection criteria and results are identical to the results of other institutions, using similar surgical techniques.
4. Since surgical technique, extent of the pelvic cellulectomy is identical between our radical hysterectomy and ART procedures, ART can be offered to patients who are fit for radical hysterectomy without adjuvant treatment.
5. Based upon these considerations, ART in stage IB cervical cancer seems to be applicable, regardless of the size of the tumor.

3.2.3. Our experience in use of Abdominal Radical Trachelectomy to treat Cervical Cancer greater than 2cm in diameter.

Our surgical technique, with regards to the extent of clearance of the tumor cell containing pelvic connective tissue, is identical to traditional radical hysterectomy (RH), apart from the preservation of the uterine corpus and adnexae. RH as a curative intent treatment is recommended in Stage IB cervical cancer by ACOG and NCCN protocols.[88] 2cm size limit has never been mentioned as a contraindication for curative intent RH surgery. The RH experience has revealed an optimum curative outcome treatment with better or at least identical disease free (DF) and overall survival (OS) to radiotherapy in larger than 2 cm tumors. [89] Our hypothesis was that oncology safety of patients diagnosed with tumors >2cm in diameter and treated by ART would be similar to cases managed by RH, in identical ICC prognosis groups.

Materials and methods

Between January 1999 and October 2006, a total of 36 patients with cervical carcinoma FIGO stage IB1-IB2 measuring greater than 2cm in diameter were explored with the intent of a fertility sparing ART and pelvic lymphadenectomy. Exclusion criteria for the fertility preserving procedure were (i) tumours less than 2cm ; (ii) metastases reported following imaging; and (iii) follow-up lasting less than 5 years. ART was completed in 22 out of 36 patients (61,1%). Every patient was followed up for more than five years. No case was lost to follow up.

Results:

22 patients' characteristics where ART was completed are listed in Table 11. Our clinical findings had to be supported by the imaging results. Lack of lymphadenopathy was a condition for ART. Patients who were found to have positive lymph nodes were excluded from the ART procedure, and were treated either with a laterally extended parametrectomy (LEP) or with adjuvant chemoradiotherapy.

14 out of 36 (38,9%) patients underwent immediate completion of radical hysterectomy based on the intra-operative findings including: positive lymph node metastasis (n=9), positive endocervical surgical margin (n=3), injury of the ovarian artery (n=1) and parametrial tumour spread (n=1). The following outcomes were recorded: average operative time - 194 minutes, estimated blood loss - 900 ml, in-hospital stay - 6 days, number of lymph nodes removed - 30-55.

Mean 5-year overall survival of ART patients was 95%. Follow-up ranged from 60 to148 months. 21 out of 22 (95%) patients who underwent ART were alive at the time of follow up. The patient who died was first diagnosed with a stage IB2 glassy cell histology tumour measuring 5cm diameter. She developed a pelvic side wall recurrence five months after ART. She was subsequently treated with chemo-radiotherapy but did not respond. A pelvic exenteration was consequently performed but the patient died of disseminated disease 16 months after the first treatment.
In contrast 6 only out of 14 (42,8 %) cases who did not match our criteria for ART surgery were alive at five years.

Median age (years)	**32,2 (24 -43)**
FIGO stage	No. of patients (%)
I/B/1 2 cm < tumor size < 4 cm	13 (59,9 %)
I/B/2	9 (40,1 %)
Hystology	
Squamous	11 (50 %)
Adenosquamous	4 (18 %)
Adenocarcinoma	1 (4,5 %)
Glassy cell	5 (23 %)
Anaplastic	1 (4,5 %)
Lymph Vascular space involvement (LVSI)	11 (50 %)

Treatment Characteristics

Median OR time (minutes)	194 (150-240)
Hospital stay (days)	6 (5-10)
Median follow-up (months)	90 (60-148)

Survival

5 year overall survival	95% (21/22)
5 year disease free survival	95% (21/22)

Table 11.

Complications post-ART

One patient (n=1; 4,5%) was diagnosed with intraoperative one-sided ureteric injury necessitating a reconstructive ureter neo-implantation with a psoas hitch procedure. Late complications included cervical stenosis (n=1; 4,5%), where the patient underwent dilatation of her neo-cervix twice before her normal menstrual pattern recovered. Stenosis of both ureters developed in the follow-up period in one patient (n=1; 4,5%), which was repaired by excision of the affected sequence of ureters, and reconstructed by the use of a small bowel conduit connecting the ureters and the urinary bladder.

Transient urinary retention necessitating a need for suprapubic or self-catheter use lasting longer than eight days was observed in five cases (22,7%). Bladder function spontaneously recovered in all cases within the first post-operative month. Constipation requiring regular laxative use to enhance defecation lasting longer than the first four weeks of follow-up were reported by four patients (18,1%). No lymphoedema was seen in this cohort of patients.

Fertility outcomes

Out of the 22 patients, eight wished to fall pregnant. One out of the eight underwent infertility treatment. Four pregnancies were recorded in three other patients. One pregnancy resulted in a first trimester miscarriage. Three pregnancies led to delivery of a healthy neonate, one at 28 weeks gestation and two at term. We must also emphasise that our follow-up in view of pregnancy rate is not complete as we could not personally contact five patients. Theoretically there may be pregnancies that we do not know about. The rest of the cohort did not fall to pregnant at the time of writing or had recently changed partners.

Discussion

The operative standard therapy for women with IB cervical cancer is still RH which was developed more than 100 years ago. The postponement of childbearing coupled with a comparatively young age at which many women are diagnosed with cervical cancer has led to

the innovation of various fertility sparing procedures.[4] Assuming the tumour does not exceed 2cm in diameter at its largest point, oncology outcomes are very promising with respect to such procedures. In tumours surpassing the 2cm threshold, the reported use of such procedures is very limited. Furthermore, VRT cannot be proposed as a treatment option for large-size tumours because of its high recurrence rate.[22,25,29,31]

In our study 36 patients diagnosed with Stage I cervical cancer measuring >2cm in diameter were surgically explored with the aim of ultimately undergoing ART. Patients that underwent ART were subsequently followed up for at least five years. The ART selection criteria applied in our series (negative surgical margins; negative lymph nodes in stage IB cervical cancer) was met by 61,1% (n=22) of our cervical cancer cases measuring >2cm in diameter. The five year survival rates for this case series (95%) are at least equal to rates reported in the literature for patients treated by radical hysterectomy +/- adjuvant therapy as the initial treatment.[93] Our survival data seems to support our hypothesis that oncological safety of ART for lesions >2cm is identical to traditional cervical cancer treatment modalities for Stage IB cervical cancer. Furthermore, the goal of performing ART as opposed to RH has been realised in four patients who have to date delivered three healthy live babies.

The relative large proportion of lymph node positivity (25%; 9/36), tumor spread to the uterine corpus (8,3%; 3/36) and occult stage IIB (2.7%; 1/36) might reflect the relative aggressive nature of cervical cancer in this very young age group.[93]

In two recent reports regarding the ART procedure, the tumour size was both <2cm and >2cm. 38% of patients (n=5) with tumour diameter >2cm had recurrent disease during a follow-up period lasting 27 months (median).[94] On the other hand *Li et al* reported that out of 14 cases who underwent ART with exophytic tumour size between 2-4cm, no evidence of recurrent disease during a follow-up period of 22.8 months was recorded.[95] Three patients received chemotherapy based on pathological findings.[95] Such significant survival differences might be the consequence of small sample sizes, short follow-up, variances in surgical radicality and the accuracy of intra-operative selection of high risk cases. Future prospective randomised trials might further explore the questions listed above. The recurrence rate of tumours >2cm has also decreased in the literature as the surgical experience of ART has increased.[93]

4. Conclusion

The aim of our study was to assess the oncologic safety of ART in large tumor patients (>2cm), compared to traditional RH or other possible first-line treatment options. Our data suggests that treatment guidelines for fertility preservation techniques have to distinguish between VRT and ART when it comes to treating relatively large (>2cm diameter) cervical cancers. VRT has been used in many centers with an excellent outcome and it may be preferred by surgeons in case of low risk tumors, such as those measuring <2cm in diameter. [22,25,29-32] However the oncology, fertility, complication risk, quality of life consequences comparison of the two radical trachelectomy techniques in less than 2 cm tumors needs to be compared in prospective trials. The appropriate treatment of tumors > 2cm is with respect to both survival and fertility outcomes remains an enigma. The extent of parametrectomy in VRT is less extensive than in Type III radical hysterectomy.[38] This might explain the lower survival witnessed following the application of VRT to treat >2cm diameter cervical cancers.[30,31] Some centers use neoadjuvant chemotherapy in "bulky" cervical cancers with the aim of downstaging before radical hysterectomy. [76,77] Currently, four approaches have been published on neoadjuvant chemotherapy and fertility sparing surgery. All the published studies were different in terms of the surgical radicality used after neoadjuvant chemotherapy. The drawback of all studies in literatures is the small sample size and the relatively short follow-up. Neoadjuvant chemotherapy in fertility sparing surgery is an experimental concept, which requires verification in the future, especially concerning oncological findings. [78-81]

Results with a completed five-year follow-up of a relatively large cohort of patients have not been published to date. Our series seem to provide more extended experience in this field. Although still preliminary, our results are encouraging and indicate that even tumors >4cm may be successfully treated with ART. We recognize that a small case series of 22 patients (such as ours) will not answer all questions regarding early-stage cervical cancer treatment. However ART applied to treat tumors >2cm appears to be safe. Future studies where ART is compared to RH with regards to management of cervical tumors >2cm might further clarify both survival and fertility outcomes.

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